PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference CP60945-2018	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/004016	International filing date *(day/month/year)* 22 March 2004 (22.03.2004)	Priority date *(day/month/year)* 21 March 2003 (21.03.2003)]
International Patent Classification (IPC) or national classification and IPC [7] C07D 498/22, A61K 31/4745, A61P 25/28		
Applicant PALUMED SA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 23 September 2005 (23.09.2005)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Ellen Moyse Telephone No. +41 22 338 89 75

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/004016	22.03.2004	21.03.2003

International Patent Classification (IPC) or both national classification and IPC
C07D498/22, A61K31/4745, A61P25/28

Applicant
PALUMED SA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/004016

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/004016

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-15

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-15 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-15 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/004016

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	-
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Clarity (Article 6 PCT)

1.1. According to formula (I) as defined in claim 1 on file -U- may represent -N (R1,R2), -COOH or -OH. However, while -U- is linked via two bonds, neither -N (R1,R2) nor -COOH nor -OH for reasons of valency can form two bonds with further residues of the molecule. Therefore, the above alternatives with -U- being -N (R1,R2), -COOH or -OH are in contradiction to the further definition of formula (I), thereby creating a lack of clarity as to the scope of protection afforded by the claims.

1.2. Similarly, double bonded -W- may represent -N (R8,R9), which has valency for only one bond.

1.3. Moreover, m2 being defined as being 0, 1 or 2 does not appear anywhere within formula (I).

1.4. On the other hand m, although being part of formula (I) is without definition.

1.5. Finally, in the embodiments of the invention, i.e. Cyclo-bi-Phen, Cyclo-tri-Phen and Cyclo-tetra-Phen (cf. application page 6-7), the phenanthroline residues are linked via a 1-3-propylene group. However, according to formula (I) as defined in claim 1 on file the linker Z comprises $-(CH_2)_n-U-(CH_2)_n-$ with n being a number from 2 to 6, i.e. an alkylene group with at least 4 carbon atoms. Thus, the embodiments of the invention do not fall within the definition of formula (I), thereby producing a lack of clarity as to the scope of the claims.

2. Support (Article 6 PCT)

The structure according to formula (I) and, thus, the subject-matter of the claims not only does not encompass the embodiments of the invention, i.e. Cyclo-bi-Phen, Cyclo-tri-Phen and Cyclo-tetra-Phen (cf. application page 6-7), but also, when defining as linker Y groups different from phenyl, goes far beyond the teaching of the application, which is restricted to phenanthren derivatives. Thus, the application as filed does not provide support for the linker Z as well as for the linker Y, when it is different from phenyl.

3. Conclusion

In view of the lack of clarity and the lack of support inherent to the linkers Y and Z of formulae (I), (II), (III) and (IV), an examination as to novelty, inventive step and industrial applicability of the claims on file is not possible. Nevertheless a

preliminary opinion on novelty and inventive step will be given for the embodiments of the invention, i.e. for Cyclo-bi-Phen, Cyclo-tri-Phen and Cyclo-tetra-Phen (cf. application page 6-7).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: MURALI DORAISWAMY P: "NON-CHOLINERGIC STRATEGIES FOR TREATING AND PREVENTING ALZHEIMER'S DISEASE" CNS DRUGS, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 16, no. 12, 2002, pages 811-824, XP009033332 ISSN: 1172-7047

D2: CHERNY R A ET AL: "AQUEOUS DISSOLUTION OF ALZHEIMER'S DISEASE ABETA AMYLOID DEPOSITS BY BIOMETAL DEPLETION" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 274, no. 33, 1999, pages 23223-23228, XP000929630 ISSN: 0021-9258

D3: CHERNY ROBERT A ET AL: "Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice" NEURON, vol. 30, no. 3, juin 2001 (2001-06), pages 665-676, XP002292658 ISSN: 0896-6273

D4: WO 98/40071 A (GEN HOSPITAL CORP ; BUSH ASHLEY I (US); ATWOOD CRAIG S (US); HUANG XUD) 17 septembre 1998 (1998-09-17)

D5: BOLDRON C ET AL: "Simple and efficient syntheses of 1,10-phenanthrolines substituted at C3 or C3 and C8 by methoxy or hydroxy groups" SYNLETT 2001 GERMANY, no. 10, 2001, pages 1629-1631, XP001183054 ISSN: 0936-5214

1. **Novelty (Article 33(2) PCT)**

The embodiments of the invention, i.e. for Cyclo-bi-Phen, Cyclo-tri-Phen and Cyclo-tetra-Phen, appear to be new in the light of the prior art available.
None of the documents cited discloses one of the exemplified compounds. The compounds being novel, their therapeutic use, the method for their preparation and their application as chelating agent are to be considered as novel as well.

2. **Inventive step (Article 33(3) PCT)**

The embodiments of the invention, i.e. for Cyclo-bi-Phen, Cyclo-tri-Phen and Cyclo-tetra-Phen, appear to involve an inventive step in the light of the prior art available.
The contribution to the art afforded with the application on file conssists in the synthesis of three different Cyclo-Phens, i.e. Cyclo-bi-Phen, Cyclo-tri-Phen and Cyclo-tetra-Phen (cf. application page 6-7), the identification of a copper-complex for two different Cyclo-Phens, i.e. Cyclo-bi-Phen and Cyclo-tri-Phen (cf. application page 7-8) and in the reduction of amyloid plaque loading in an

Alzheimer's disease transgenic mouse model (cf. application page 9-11).
The closest prior art D1 (page 819-820, paragraph entitled "1.9. Chelation Therapy"), D2 (page 23227-23228, paragraph entitled "Discussion"), D3 (page 670-673, paragraph entitled "Discussion") and D4 (claim 8) discloses the use of Zn/Cu chelating agents such as clioquinol, EGTA, TPEN, BC, TETA etc. for the treatment of neurodegenerative diseases. None of the documents discloses Cyclo-bi-Phen, Cyclo-tri-Phen and Cyclo-tetra-Phen.
Thus, the objectivetechnical problem to be solved in the light of D1-D4 was to provide alternative therapeutics for the treatment of neurodegenerative diseases.
None of the prior art documents available discloses Cyclo-bi-Phen, Cyclo-tri-Phen and Cyclo-tetra-Phen. Only D5 (figure and scheme 2) discloses 3-Clip-Phen and 3-propyl-Clip-Phen. However, the structure of Cyclo-bi-Phen, Cyclo-tri-Phen or of Cyclo-tetra-Phen was not obvious from D5.